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The Commissioner of Patents

18 August 2004

Madam

IN THE MATTER OF International Patent Application No. PCT/AU2003/001058
in the name of ROYAL WOMEN'S HOSPITAL
Entitled MARKER FOR CANCER
Our Ref: AJS:AJH:RMB:FP18268

We refer to the Written Opinion dated 1 April 2004 issued by the International Preliminary Examining Authority in respect of this application.

In response to the Examiner's objection that the claims of this application are not novel or inventive in the light of cited prior art, the applicant respectfully draws the Examiner's attention to the passage at page 4, lines 23 to 28 of the specification, and points out that the present invention is based on the discovery of a cell-free immunoreactive form of integrin linked kinase (irILK). As stated at page 9, lines 14 to 19 of the specification, this new form of ILK is secreted from intact cells into medium perfusing the cells. In contrast, the previously known form of ILK is detected in tissues or after cell lysis. Therefore, the new form of ILK clearly differs from the previously known form in its location within an animal. There are very few examples of an intracellular cytosolic protein being secreted, and the present inventors were surprised to find irILK in the biological fluid of cancer patients.

The discovery of a cell-free form of ILK provides the advantage that biological fluid from a subject can be tested for the presence of irILK. As stated on page 13, lines 26 to 32 of the specification, biological fluids include whole blood, plasma, serum, peritoneal fluid, ascities, tissue conditioned medium, urine, tears, etc. Before the discovery of the cell-free form of irILK by the present inventors, it was believed that ILK was present only in the tissues of cancer patients, and therefore biopsy samples were required in order to diagnose cancer or monitoring the efficacy of cancer treatment. Clearly, the use of biological fluids for determining the presence of ILK has advantages over the use of biopsy samples.

None of the prior art cited by the Examiner discloses or suggests a cell-free immunoreactive form of ILK. Specifically, D1 and D2 disclose the activity of ILK in the regulation of a cytoplasmic pathway and therefore disclose the intracellular form of ILK. This is not the cell-free form of ILK of the present invention. D3 discloses that ILK is located inside a cell and uses biopsy-derived samples in order to diagnose ILK activity. Therefore, D3 discloses the intracellular form of ILK, not the cell-free form of the present invention. D4 is discussed in

the specification as filed, at page 3, lines 14 to 24. As discussed in this passage, the ILK molecule of D4 interacts with the cytoplasmic domains of β1 and β3 intergrin subunits. Therefore, D4 discloses the intracellular form of ILK, not the cell-free form of the present invention. D5 discloses the modulation of ILK expression in tissues and tumors. D5 does not disclose the cell-free form of ILK as the new form is present in the medium perfusing cells and does not require an analysis of tissue or products of cell lysis.

Thus, all of the cited documents disclose the intracellular form of ILK which may be detected in tissues or after cell lysis. None of the cited documents disclose or suggest a form of ILK which is secreted from intact cells into medium perfusing the cells. This new form of ILK is surprising and unexpected.

Accordingly, independent claims 1 and 6 to 9 of the present application, and claims dependent therefrom, are novel and inventive in the light of the cited prior art.

Favourable reconsideration is requested. If despite the above arguments the Examiner is minded to issue an unfavourable International Preliminary Examination Report, we request a further written opinion.

Yours faithfully

PATENT COOPERATION TREATY

DIARIED
ID 321831

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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GRIFFITH HACK
14 SEP 2004
1 Bec YM
2 AJS

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	14 SEP 2004
Applicant's or agent's file reference AJS:AJH:RMB:FP18268	**REPLY DUE** within **ONE Month** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001058	20 August 2003	20 August 2002

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C07K 14/47; 16/18; C12N 9/12; G01N 33/53; A61K 39/395; A61P 35/00

Applicant
ROYAL WOMENS HOSPITAL et al

1. This written opinion is the **second** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[X]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The **FINAL DATE** by which the international preliminary examination report must be established according to Rule 69.2 is:
20 December 2004

4. The applicant is hereby **invited to reply** to this opinion.

When? See the **Reply Due** date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the **Final Date** by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least **3 months before the Final Date** by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

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WRITTEN OPINION

International application No.
PCT/AU2003/001058

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

WRITTEN OPINION

International application No.
PCT/AU2003/001058

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: **15, 16, 18 and 19 .**

because:

☐ the said international application, or the said claim Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **15, 16, 18 and 19**

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2	YES
	Claims	1, 3-25	NO
Inventive step (IS)	Claims	2	YES
	Claims	1, 3-25	NO
Industrial applicability (IA)	Claims	1-25	YES
	Claims		NO

2. Citations and explanations

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 Proc Am Assoc for Cancer Research (March, 2002)
D2 ibid, (2001)
D3 WO 1997/23625
D4 Trends in Cell Biology (1999)
D5 US 6177273

Novelty (N) and Inventive Step (IS) Claims 1 and 3-25

The present invention relates to a marker for cancer and use of this marker in methods of diagnosis and monitoring and treatment of cancer.

Claim 1 recites a claim to a cell-free immunoreactive Integrin Linked Kinase (ILK). Claim 2 is appended to claim 1 and recites the 59 kDa kinase.

Claim 6 recites a method of detection of cancer comprising determining the presence or absence of irILK in a sample of a biological fluid.

However, it appears that the prior art documents D1-D5 clearly disclose and teach the present invention.

D1 discloses and teaches the involvement of integrins, including ILK in cancer cells proliferation. The subject matter of the cancer cells include ovarian cancer. Therefore claims 1 and 19 and the appended claims are anticipated by D1.

D2 discloses and teaches the implication of ILK in ovarian cancer cells. Moreover, the 59kDa kinase, the subject matter of claim 2 of the present invention, is clearly disclosed in D2.

D3 discloses and teaches ILKs and their role in cell modulation. The 59kDa protein is also disclosed at page 6.

D4 discloses and teaches ILKs and the 59kDa protein kinase, and its role in signal transduction, and its association with tumorigenesis (p320).

D5 discloses and teaches ILKs and its over-expression in certain tumours (column 1).

(continued in Supplemental Box)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 15, 16, 18 and 19 are not fully supported by the description.

These claims defined "agents" which are capable of modulating ILK. However, the structural features of the agents is not defined.

Therefore these claims are not fully supported by the description.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

The applicant submits that none of the documents D1-D5 disclose or suggest a cell-free immunoreactive form of ILK. However, the characteristics of ILK are not clearly defined in claim 1. There is no indication that the cell-free ILK of the present invention is distinct from the prior art.

It may be that the specific ILK as defined in claim 2 may be novel. However, in the absence of any definition of the ILK and properties of this ILK that are distinct from the prior art, claims 1 and 3-25 are not novel.

Further, it would appear that the skilled addressee would be led to other aspects of the invention in respect to the method and kit claims as a matter of routine, following the teaching in the art according to any one of D1-D5.

Therefore the invention as defined in claims 1 and 3-25 is not novel and lacks an inventive step.